(2)

AD-A234 589

ORT DOCUMENTATION PAGE

1a	1b RESTRICTIVE MARKINGS
2a SECURITY CLASSIFICATION AUTHORITY	3 DISTRIBUTION / AVAILABILITY OF REPORT Approved for public release; Unlimited distribution.
2b DECLASSIFICATION / DOWNGRADING SCHEDULE	
4 PERFORMING ORGANIZATION REPORT NUMBER(S)	5 MONITORING ORGANIZATION REPORT NUMBER(S) AFOSR-TR- 91 0210
6a NAME OF PERFORMING ORGANIZATION Hatfield Marine Science Center Oregon State University	6b OFFICE SYMBOL (If applicable)
	7a NAME OF MONITORING ORGANIZATION Air Force Office of Scientific Research/NL
6c ADDRESS (City, State, and ZIP Code) Marine Science Drive Newport, OR 97365	7b ADDRESS (City, State, and ZIP Code) Building 410 Bolling AFB, DC 20332
8a NAME OF FUNDING / SPONSORING ORGANIZATION AFOSR	8b OFFICE SYMBOL (If applicable) NL
	9 PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER AFOSR-89-0262
8c ADDRESS (City, State, and ZIP Code) Building 410 Bolling AFB, DC 20332-6448	10 SOURCE OF FUNDING NUMBERS

PROGRAM ELEMENT NO	PROJECT NO.	TASK NO	WORK UNIT ACCESSION NO
61102F	2312	A1	

11 TITLE (Include Security Classification)
Parallel Processing and Learning: Variability and Chaos in Self-Organization of Activity in Groups of Neurons

12 PERSONAL AUTHOR(S)
George J. Mpitsos, PI

13a TYPE OF REPORT	13b TIME COVERED	14 DATE OF REPORT (Year, Month, Day)	15 PAGE COUNT
Annual Report	FROM 1/14/90 TO 1/13/91	1991, March, 8	8

16 SUPPLEMENTARY NOTATION

17 COSATI CODES			18 SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
FIELD	GROUP	SUB-GROUP	Parallel Processing, Neural Networks, Backpropagation, Neurotransmitters, Acetylcholine, GABA, Serotonin, Enkephalins, Dynamical Systems, Chaos, Immunohistochemistry

19 ABSTRACT (Continue on reverse if necessary and identify by block number)

Three interrelated lines of work have been pursued resulting in 7 papers already accepted or submitted to journals, 7 more presently being written, and 2 review articles. A fourth line of work has been on the development of analytical tools.

1. NEUROTRANSMITTERS. We have examined the immunohistochemical localization of over 12 different neurotransmitters in all of the nervous system components of two different marine molluscs, *Aplysia* and *Pleurobranchaea*. To do this for each neurotransmitter, we made complete serial histological sections of all major ganglia in each nervous system. Localizations were performed using immunohistochemistry and fluorescence microscopy. Since many of the commercially available antisera proved to be nonspecific, we generated 11 antisera in our laboratory. One of the major achievements occurred in our work on acetylcholine, which our previous AFOSR-funded work implicated as having an important role in associative learning in *Pleurobranchaea* through muscarinic receptors. Our acetylcholine immunofluorescence is the first reliable method available anywhere for visualizing the

20 DISTRIBUTION / AVAILABILITY OF ABSTRACT	21 ABSTRACT SECURITY CLASSIFICATION
☒ UNCLASSIFIED/UNLIMITED ☒ SAME AS RPT ☐ DTIC USERS	Unclassified
22a NAME OF RESPONSIBLE INDIVIDUAL Dr. Genevieve Haddad	22b TELEPHONE (Include Area Code) (202) 767-5021
	22c OFFICE SYMBOL NL

DD FORM 1473, 84 MAR — 83 APR edition may be used until exhausted. All other editions are obsolete.

SECURITY CLASSIFICATION OF THIS PAGE
UNCLASSIFIED

Item 19 Abstract, continued:

location of acetylcholine, and has proved positive not only in invertebrates, but also in mammalian central and autonomic nervous tissues.

A second major finding also complements our previous AFOSR-funded work. The previous studies demonstrated that adaptive neurobehavioral patterns of activity emerge dynamically and variably through a highly interconnected network; i.e., that the network itself can not be used to predict what the behavior or pattern will be. The same is true of our examination of neurotransmitters. There is such extensive divergence and convergence of multiple neurotransmitters systems onto similar areas in the brain that many neurohumoral factors may not be motor- or sensory-specific. We have proposed that the neurohumoral factors form a nonlinear dynamical shell that controls the underlying electrical properties of the network. Thus, there are two interacting levels of self-organization in multiply converging biological networks: one of these is electrical in accordance with the underlying network connectivity; the other is neurohumoral. Examination of either of these using classical methods that isolate individual components may give reliably predictable results, but may not provide insight into the mechanisms that actually produce the adaptive neural or behavioral responses.

2. NEURAL NETWORKS. Neural network (backpropagation) computer simulations were used (a) to examine some of the fundamental principles that emerge from converging and diverging connections, and (b) to demonstrate the utility of our new time-invariant noise control algorithm (TINA) for generating response optimizations. In (b) we compared TINA against simulated annealing. TINA is event-dependent whereas simulated annealing is time-dependent. Since adaptive systems are generally event-dependent TINA is easier to implement and better suited to studies of biological systems, and for use in adaptive robotic systems, than is simulated annealing. The studies in both (a) and (b) suggest many lines of experimentation that would otherwise have been difficult if not impossible to obtain from the more complex biological systems themselves.

3. VISUALIZATION OF SPATIO-TEMPORAL ACTIVITY. We have begun our attempt to develop computer visualization tools for examining the spatial as well as the temporal responses of multicomponent systems. As a start, the work uses hypercycle theory of molecular systems. Nonetheless, the methodology (presently at the level of bifurcation analysis of dynamical states) has some applicability to neural networks. Our goal is to tie together the above findings of convergence and divergence in network architectures and neurohumoral systems using spatially distributed hypercycles and "real-time" control of their dynamics.

4. ANALYTICAL TOOLS. This consists of computer programs that we use to analyze dynamical systems. We call this the "Chaos User's ToolKit", but chaos is not be an essential feature of the system being examined. Although the ToolKit does not represent journal publications, we distribute the programs to laboratories internationally. The ToolKit will eventually contain all of our spatio-temporal methods.

CONCLUSION: Our work over the past year is consistent with the ideas we have consistantly expressed and researched under AFOSR funding: The work shows that a new theoretical foundation is needed with which to handle the internal workings of distributed, multicomponent systems, whether these systems are biological or machine. Work in a particular system, *Pleurobranchaea, Aplysia*, lobster, or even mammalian brain is only of secondary importance. A new dynamical theory is essential with which too handle data and guide research. Computer graphics may provide some insights into new theoretical approaches.

I. OVERVIEW

The work for all of the 14 papers listed below has already been done. Seven papers are already accepted by journals or sent to them. The other seven are presently aggressively being written for submission to journals. In addition, the list contains two review articles, both of them invited by the editors.

The publications fall into three major areas: (1) Immunohistochemistry, (2) Neural Network Computer Simulations, and (3) work on hypercycles.

A fourth area is listed under Dynamical Systems Analytical Tools. This fourth area does not consist of journal publications (although a book is presently being considered at the request of VCH publishers). The ToolKit is a growth of our own laboratory needs, but has been requested by other laboratories. As a service, we supply the programs and source code to other laboratories free of charge.

The two **Neural Network** papers were originally requested by a new journal during the first year of the present grant. The journal (**Order and Chaos**; Chief Editor: Ralph Abraham) accepted the papers. But when the journal failed to meet its financial birth, we submitted them to Neural Networks. One paper has been accepted. The other has been revised and resubmitted.

1. Comments on Immunohistochemistry:

List of Publications: Section II (A 2-3; B 2; C 1-2; D 3-7).

The Immunohistochemistry consists of examination of over 12 different neurotransmitters. Each transmitter was examined in complete serial histological sections in all ganglia of the molluscs *Aplysia* and *Pleurobranchaea*. We soon learned that many of the "high quality" antisera available commercially are not sufficiently specific for the intended cytochemical recognition. Therefore, we ourselves had to generate many of the antisera in our own laboratory.

Our own laboratory-generated antisera are listed in Section III.

a. First Major Immunohistochemical Achievement:

Antisera against acetylcholine and appropriate fixation methods were developed. Acetylcholine is of interest to many different researchers dealing both with human physiology/diseases and animal experimental models.

Uniqueness: Our antisera and fixations provide the first reliable methods for immunofluorescent visualization of acetylcholine in both invertebrate and mammalian tissues.

Despite its importance and the fact that many laboratories have for decades tried to detect acetylcholine using immunofluorescence, no reliable methods have been available. The Geffard methods (Geffard, M., A. McRae-Degueurce, and M. L. Souan. 1985.

Immunocytochemical detection of acetylcholine in the rat central nervous system. **Science 229:** 77-79.) proved to be highly error-prone. Their antisera have been removed from the market.

Papers are presently being written for publication, as listed below. An initial announcement is presented in our summary of many of our findings in the article listed under Papers Revised and Resubmitted (B2).

Purpose: We developed the methods because our previously-funded AFOSR work showed that the muscarinic cholinergic nervous system is important in enhancing learning in our experimental animal. This previous AFOSR-funded work appeared in the following Publications:

Mpitsos, G. J., T. F. Murray, H. C. Creech, and D. L. Barker. 1988. Muscarinic antagonist enhances One-trial food-aversion learning in *Pleurobranchaea*. **Brain Res Bull 21:** 169-179.

Murray, T. F., and G. J. Mpitsos. 1988. Evidence for heterogeneity of muscarinic receptors in the mollusc *Pleurobranchaea*. **Brain Res. Bull. 21:** 181-190.

Murray, T. F., G. J. Mpitsos, J. F. Siebenaller, and D. L. Barker. 1985. Stereoselective L-[^{3}H] Quinuclidinyl Bensilate-binding sites in nervous tissue of *Aplysia californica*: Evidence for Muscarinic Receptors. **J. Neurosci. 5:** 3184-3188.

Therefore, one of the tasks has been to identify and visually locate cholinergic neurons. We now have a reliable method for doing that.

A future goal will be to devise immunohistochemical methods for visually locating the muscarinic postsynaptic cells.

The long-term goal is to examine the identified presynaptic and postsynaptic cells before, during, and after training animals to perform associative learning tasks.

b. Second Major Immunohistochemical Achievement:

In keeping with our previous AFOSR-funded work (e.g. Mpitsos, G. J., and C. S. Cohan. 1986. Convergence in a distributed motor system: Parallel processing and self-organization. **J. Neurobiol. 17:** 517-545.) The immunohistochemistry has shown that there is perfuse divergence and convergence of neurotransmitter systems onto similar large areas in the brain. These findings are consistent with the notion that there is little motor-specific neurotransmitter projection. We have proposed (e.g. Coinila, S., and G. J. Mpitsos. 1991. Immunohistochemistry of diverging and converging neurotransmitter systems in molluscs. **Biol. Bull. Revised & ReSubmitted**.) that (1) all or most of these transmitter systems may be active at the same time, and that (2) the specificity of neurohumoral action emerges dynamically (and in an error-prone fashion) through the aggregate actions.

That is, just as the neuroelectrical activity can not be predicted from the particular anatomic connections of the classical "neurocircuits" that most people still like to draw, so

it is that the neurohumoral effects may not be predictable from experimentally isolated actions of individual neurotransmitters.

The neurohumoral interactions, therefore, form a second shell of nonlinear control over the neuroanatomic connections. The first dynamical shell arises from the electrical properties. The second shell arises from the aggregate neurohumoral control of the electrical properties. One possibility is that the neurotransmitters may affect the bifurcation properties of the underlying connectivity. However, to understand this properly, we must, again, deviate our analysis away from experimental approaches that control only one transmitter at a time.

c. Conclusion To The Immunohistochemistry.

The conclusion that we have brought forth in our work is that an understanding of both the neuroelectrical and the neurohumoral aspects of the nervous systems requires statistical mechanical theories rather than the typically applied notion of the "neurocircuit".

As we have addressed in our previous neurobehavioral work (see references over the past six years) these statistics may be deterministic, as in chaos and limit cycles, or nondeterministic, as in random noise or other high-dimensional factors. Our neural network studies (described below) address the random chaotic and random factors in detail .

1. Comments on Neural Network Studies:

Two types of neural network studies have been accepted or submitted for publication:

1. Time-Invariant Noise Algorithm (TINA) in publication II, A1, listed below.

Random noise may be an important factor to control when the systems seek to optimize their responses. Simulated Annealing has typically been used for such optimizations. However, simulated annealing is time-dependent. Adaptive systems can not be time-dependent because their environments are not necessarily predictable. Adaptive systems, therefore, are event-dependent. Robert Burton and I devised a set of time-independent noise algorithms, as represented by TINA, for application to adaptive systems.

The results of TINA are generally better than in simulated annealing, and easier to implement.

An unexpected finding was that networks that learned in the presence of noise, later learned better in a new task when no noise was present. Examination of the synaptic weights set during learning in these networks demonstrated that the post-noise enhancement of learning could not be accounted on the basis of statistical differences in the synapses. Yet, of course, the effect had to be stored in the synapses (and thresholds). We proposed that the effect could be explained on the basis of error-surfaces that the

networks must traverse during learning. When the task in the post-noise training has error-surface similarities to the task required of the network when noise is present, network learning in the second task is enhanced. Thus, it appears, the exposure to noise in during learning of the first task allowed the network to set its synapses in response to many different view of the error surface as it appeared from trial to trial during training. Although networks that were not exposed to noise during the first task eventually performed as error-free as the noise-exposed networks, the noise-free environment did not allow the network to become exposed to as much of the error-surface as occurred in networks that experienced noise. Noise produced more error, but allowed the network to see more of its potential universe. The reviewer of the paper suggested that this process might be termed a form of "metaknowledge"; we liked his suggestion, and incorporated the term into the paper.

The real importance of such phenomena as "metaknowledge" is that they point out the need to begin to view network functions using new language. Classical neurocircuit persective could not have accounted as easily for the findings.

2. Convergence and Divergence: Emergent properties having analogy to biological systems.

Publication II, B2, stresses the same network characteristics as in our physiological work (e.g, see Mpitsos, G. J., and C. S. Cohan. 1986. Convergence in a distributed motor system: Parallel processing and self-organization. **J. Neurobiol. 17:** 517-545.).

The findings in our neural network paper are too numerous to summarize here, but show that biological work must address a variety of features that have not been addressed heretofore. For example: (1) Trainable thresholds (not just trainable synaptic weights) are critically important. (2) Weak ("lazy") synapses are extremely important, and may act as temporary "computational registers". They are needed for learning occur but are not needed after a particular task is learned. Nonetheless, they are need if new tasks are to be learned. (3) The dynamics of input signals are extremely important, even in networks that learn nothing about the dynamics itself. (4) Biologists must begin thinking of response error-surfaces. If the latter is true, it is necessary to determine whether biological systems seek optimal energy states, and, especially, whether such optimal states involve gradient descents in error or energy.

3. Hypercycles.

Work has begun, and two papers are presently being written (II, D1-D2), on the application of hypercycle theory to neural networks. The purpose of such studies are to develop computer graphics methods for visualizing how groups of neurons work together. This work is an intermediate step between the non-dynamical neural network studies (II: A1, B1) and visualization of the spatial temporal flow of activity occurring in real biological systems and in simulation models having realistic characteristics.

Work on hypercycles is being done in collaboration with Dr. Frederico Moran, Department of Biochemistry, University of Madrid.

4. The Computer Analytical Tools: "Chaos User's ToolKit"

For a description of some of the major tools we have programmed into the ToolKit, see Section IV below.

II. PUBLICATIONS

A. Papers Published or Accepted for Publication:

1. Burton, R. M., and G. J. Mpitsos. 1990. Event-dependent control of noise enhances learning in neural networks. **Neural Networks. In Press.**

2. Soinila, S., G. J. Mpitsos, and P. Panula. 1990. Comparative study of histamine immunoreactivity in nervous systems of *Aplysia* and *Pleurobranchaea*. **J. Comp. Neurol. 298:** 83-96.

3. Soinila, S., N. Bäck, and G. J. Mpitsos. 1990. Distribution of Met(5)-Enkephalin-Arg(6)-Gly(7)-Leu(8) immunoreactivity in the rat and mouse pituitary gland **Regulatory Peptides. In Press:** .

B. Papers Revised & Resubmitted:

1. Mpitsos, G. J., and R. M. Burton. 1991. Convergence and divergence in neural networks: Processing of chaos and biological analogy. **Neural Networks Revised & ReSubmitted.**

2. Soinila, S., and G. J. Mpitsos. 1991. Immunohistochemistry of diverging and converging neurotransmitter systems in molluscs. **Biol. Bull. Revised & ReSubmitted.**

C. Papers Submitted:

1. Soinila, S., and G. J. Mpitsos. 1991. Binding of fluorochromes in neuroendocrine cells of the *Aplysia* cerebral ganglion. **Neuroscience. Submitted.**

2. Soinila, S., G. J. Mpitsos, and J. Soinila. 1991. Enkephalin immunohistochemistry: Model studies on conjugation reaction and fixation. **Histochemistry. Submitted:** .

D. Papers Presently in Preparation:

1. Mpitsos, G. J., F. Moran, and H. C. Creech. 1991. Geometry of hypercycle dynamics.

2. Moran, F., M. A. Andrade, F. Montero, and G. J. Mpitsos. 1991. Mathematical analysis of of dynamical states in hypercycle systems.

3. Soinila, S., J. Gerke, N. Bäck, and G. J. Mpitsos. 1991. Distribution of acetylcholine-containing nerve fibers in the rat pituitary gland. .

4. Soinila, S., and G. J. Mpitsos. 1991. Colocalization of the neuropeptides FMRF-amide and SCPB in nervous systems of *Aplysia* and *Pleurobranchaea*. .

5. Soinila, S., and G. J. Mpitsos. 1991. Distribution of acetylcholine in the nervous system of *Aplysia* and *Pleurobranchaea*.

6. Soinila, S., and G. J. Mpitsos. 1991. Vasoactive intestinal polypeptide immunoreactivity in the nervous system of the marine molluscs *Aplysia* and *Pleurobranchaea*.

7. Soinila, S., G. J. Mpitsos, P. Panula, and I. Virtanen. 1991. Gamma-amino butyric acid (GABA) in nervous systems of *Aplysia* and *Pleurobranchaea*: Immunohistochemical localization.

E. REVIEWS

1. Mpitsos, G. J. 1990. Book Review of: *Neural Connections, Mental Computations*. L. Nadel, L. A. Cooper, P. Culicover, R. M. Harnish, eds. Cambridge, MIT Press (1989), 355 pp. **Neural Networks 3:** 237-241.

2. Mpitsos, G. J. 1991. Chaos in brain function. pp. in **Neuroscience Year,** Birkhauser Boston, **In press.**

III. ANTISERA PRODUCED IN OUR LABORATORY

1. 3 polyclonal antisera against ACETYLCHOLINE.
2. 3 polyclonal antisera against SEROTONIN.
3. Polyclonal antiserum against GAMMA-AMINOBUTYRIC ACID.
4. 2 polyclonal antisera against ENKEPHALIN-OCTAPEPTIDE (MEAGL).
5. Polyclonal antiserum against CARBACHOL-PROTEIN CONJUGATE.
6. Polyclonal antiserum against GLUTARYLATED HEMOCYNANIN.

IV. DYNAMICAL SYSTEMS ANALYTICAL TOOLS

1. Computer methods for visualizing and analyzing time series data: "The Chaos User's ToolKit". The following is a list of some of the tools the Kit contains.

i. Time series (multichannel) display.

ii. Manual strobe between displayed channels.

iii. Grassberger-Procaccia Algorithm for calculating attractor dimension.

iv. Wolf's Algorithm for estimating the principal Lyapunov exponent of a time series.

v. Wolf's Algorithm for calculating the full spectrum of Lyapunov exponents from a system of ordinary differential equations.

vi. Poincaré sections of 2-Dimensional maps.

vii. 1-Dimensional maps of Poincaré sections.

viii. Time series generators of model systems for testing tools.

ix. Autocorrelation function.

x. High-resolution PostScript 3-D displays of phase portraits using color-scales, gray-scales, or line thickness to show depth.

As a service to other laboratories internationally, we provide these programs at no cost. We continually update the programs as we use them ourselves.

All of them are written for the Apple Macintosh and are generally run using pull-down menus.

The programs are accompanied by a continually updated manual. Source code is also available on request.

The ToolKit will eventually contain all of our computer visualization methods on spatial and temporal activity of distributed systems.